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Pneumococcal meningitis in Iran: a systematic review and meta-analysis

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ABSTRACT

Objective: To estimate the frequency of pneumococcal meningitis among patients with bacterial meningitis in Iran.

Methods: PubMed, Embase, Web of Science and Scientific Information Database (www.sid.ir) were searched from 2000 to 2016 to identify studies on the frequency or prevalence of pneumococcal meningitis in Iran. Stata 14.0 (StataCorp, College Station, Texas, USA) was used to analyze the data.

Results: Of the 131 records identified from the databases, 21 studies fulfilled the eligibility criteria. The analyses showed that 25.0% (95% *CI*: 19.0-32.0; I^2=71%) of the confirmed bacterial meningitis (including children and adults) cases were caused by pneumococcus.

Conclusions: The large fraction of meningitis cases caused by pneumococcus demonstrates that pneumococcal meningitis is a major public health problem in Iran, and the introduction of pneumococcal vaccines merits further attention from health authorities.

1. Introduction

Streptococcus pneumonia (*S. pneumoniae*) is an important pathogen causing serious illnesses such as sepsis, meningitis, and pneumonia[1-3]. This Gram-positive bacterium is one of the most common pathogens of bacterial meningitis in children younger than 2 years worldwide[4]. Pneumococcus causes 10% to 60% of meningitis cases among patients in different age groups, but the incidence is higher in adults patients than in children[5,6]. Other pathogens [*i.e.* group *B streptococcus*, *Escherichia coli*, *Listeria monocytogenes*, *Haemophilus influenzae* type b (Hib), and *Neisseria meningitides*] account for most cases of bacterial meningitis in children younger than 2 years; however, the causes of this age pattern are not fully understood[7-9]. In recent years, despite advances in infection treatment strategies, the overall frequency of death associated with bacterial meningitis was between 19% to 37%[10,11]. Antibiotic-resistance and treatment failure is a major concern, as 15%-30% of *S. pneumoniae* strains have become multidrug resistance[12-14]. Despite antibiotic treatment, some of the patients showed significant side effects including seizures, cognitive impairment, hearing loss and other deficiencies[15].

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The epidemiology of bacterial meningitis has been changed by several preventive measures introduced since the early 1990s, such as the introduction of the Hib conjugate vaccines and the pneumococcal conjugate vaccines for infants[16]. Although Hib and pneumococcal vaccines have been available for more than a decade in developed countries, they have only recently been available to children in low-income countries[17]. Iran does not yet use pneumococcal vaccinations routinely. Recommendations have been provided for the targeted use of the 23-valent pneumococcal polysaccharide vaccine and PCV13 among people with underlying medical conditions that increase their risk for contracting pneumococcal disease or experiencing complications of pneumococcal disease if infected. In USA, the incidence of pneumococcal meningitis in children aged <2 years has declined from 7.7% to 2.6% following the introduction of PCV[18]. Since the epidemiology of pneumococcus varies with time and geographic area, the local incidence of pneumococcal meningitis is useful for health care decision-makers. Therefore, this study was designed to analyze the national data of pneumococcal meningitis in Iran using a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Statement[19].

2. Materials and methods

2.1. Information sources and search strategy

A literature search of the bibliographic database, including PubMed, Embase, Web of Science and Scientific Information Database (www.sid.ir), was performed from 2000 to 2016. The search strategies were based on the following search terms: (*Streptococcus pneumoniae* OR *S. pneumonia* OR pneumococcus) AND (meningitis) AND (Iran). This combination of terms was used for searching in article title, abstract or keywords. Reference lists of selected articles (backward citation) and the relevant articles found during the initial search were searched and forward citation tracking was carried out, to identify further relevant studies. The records found through database searching were merged and the duplicates and overlap of patient population and date of the study were removed using EndNote X7 (Thomson Reuters, New York, NY, USA). The records were initially screened by title and abstract to exclude those not related to the current study. Then the full-text of potentially eligible records were retrieved and examined.

2.2. Inclusion and exclusion criteria

Studies were included if they met all of the following criteria:(1) Studies evaluating bacterial meningitis; (2) Reporting standard laboratory-confirmed bacterial meningitis (cerebrospinal fluid culture) and (3) Presenting the frequency of *S. pneumoniae*.

Our exclusion criteria were: (1) Data on bacterial meningitis and *S. pneumoniae* were not available; (2) Nonstandard methods were used for diagnosis of bacterial meningitis (*e.g.* clinical presentation of patients), and (3) Data were restricted to viral meningitis.

2.3. Data extraction

The following items were extracted from each article: first author, publication date, study year, place of study, study sample size, patients' age, diagnostic methods, the number and the prevalence or frequency of patients with *S. pneumoniae*. Any disagreements or discrepancies were resolved in consensus with a third investigator.

2.4. Quality assessment of studies

We assessed the study quality by using a checklist provided by the Joanna Briggs Institute[20].

2.5. Statistical analysis

For each study, the overall frequency of *S. pneumoniae*, and the corresponding standard errors and 95% confidence intervals (95%*CI*) were calculated. Analyses were performed using random-effects weights. In order to estimate a pooled effect, we utilized the "metaprop" command. We used "ftt cimethod" (score) or Freeman-Tukey transformation procedures for collecting binomial data. The between-study heterogeneity was assessed by using Cochran's Q, and the I^2 statistic and Galbraith graph. To check for publication bias, we used Egger's and Begg's tests (P<0.05 was considered indicative of statistically significant publication bias). All the analyses were conducted using Stata 14.0 (StataCorp, College Station, Texas, USA).

3. Results

3.1. Study selection

A total of 131 articles were found in the initial search, of which 87 records were screened by title and abstract, 31 full-text articles were reviewed, and 21 studies were included in the final analysis (Figure 1).

3.2. Study characteristics

Table 1 summarizes the main characteristics of the included studies[21-41]. In all included studies, bacterial meningitis was confirmed by cerebrospinal fluid culture as the gold standard method. Standard microbiological procedures were used to assign the isolated bacteria to species. All of the included observational studies reported the frequency of *S. pneumoniae* among patients with bacterial meningitis. A total of 1 022 patients with bacterial meningitis were included in the meta-analysis. In all included studies, hospital-acquired pneumonia was not diagnosed in patients.

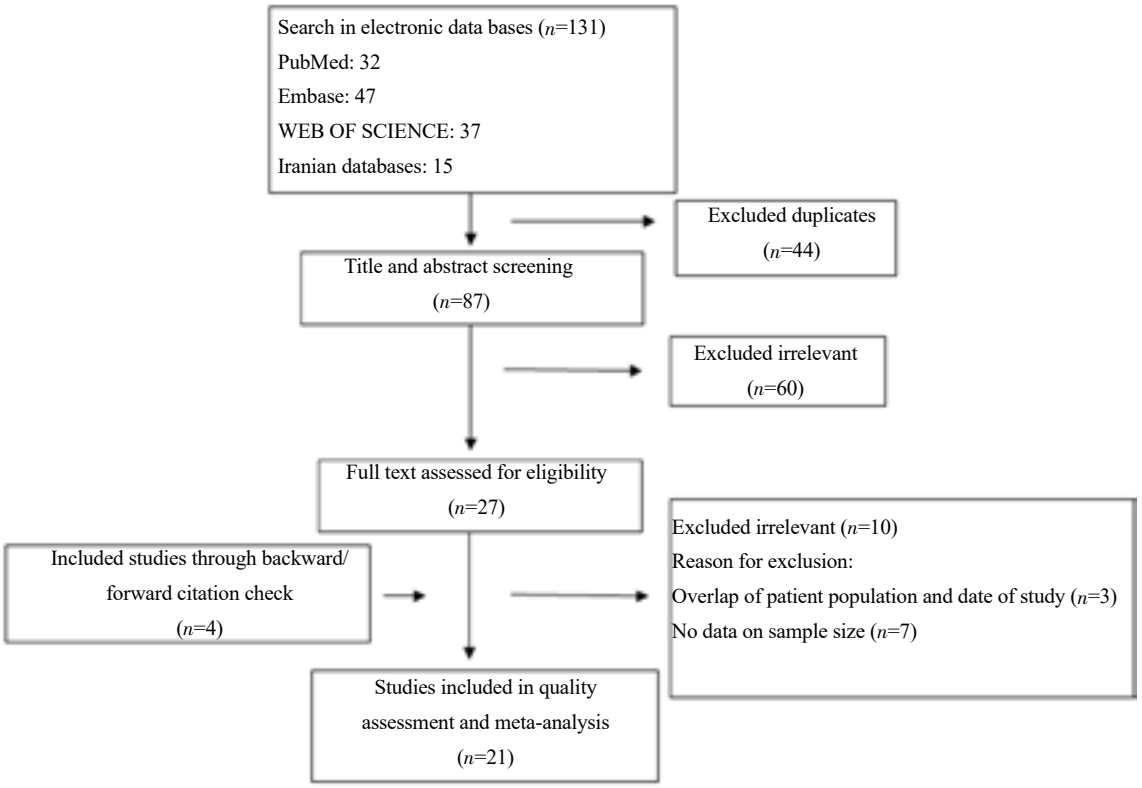

Figure 1. Flow diagram of review process and study selection.

Table 1. Characteristics of the included studies investigating frequency of *S. pneumoniae* among Iranian patients with confirmed bacterial meningitis.

First author	Publication date	Study duration	City	Suspected cases	Abnormal lumbar puncture	Confirmed bacterial meningitis	Total No. of *S. pneumoniae*	Neonates included
Abdi [21]	2005	1991-2000	Tehran	NA	NA	131	40	No
Zamani [22]	2005	1994-1999	Tehran	294	NA	15	1	Yes
Ehsanipour [23]	2004	1997-2002	Tehran	245	9	4	2	No
Aletayeb [24]	2010	1997-2007	Ahvaz	NA	NA	31	0	Yes
Ghaemi [25]	2001	1999-2000	Gorgan	100	NA	7	3	No
Tavasoli [26]	2014	2000-2010	Tehran	422	19	7	3	No
Haghiashteiani [27]	2008	2001-2007	Tehran	1 800	NA	121	21	Yes
Qurbanalizadegan [28]	2010	2002-2006	Tehran	NA	130	36	13	Yes
Kanani [29]	2005	2002-2005	Sanandaj	161	NA	14	3	No
Bahador [30]	2009	2003-2005	Kerman	NA	126	12	3	No
Alavi [31]	2010	2003-2007	Ahvaz	569	312	42	16	No
Abdinia [32]	2014	2003-2013	Tabriz	7 112	NA	107	37	Yes
Ataee [33]	2010	2005-2009	Tehran	NA	270	171	61	No
Heydarian [34]	2014	2005-2012	Mashhad	453	80	5	1	No
Bagheri [35]	2015	2006-2012	Sari	NA	137	14	7	No
Ghadiri [36]	2014	2007-2009	Kermanshah	NA	NA	11	4	No
Rezaie [37]	2013	2008-2009	Tehran	NA	55	11	0	Yes
Mahmoudi [38]	2013	2009-2011	Tehran	NA	31	20	7	No
Yousefi [39]	2014	2009-2013	Hamadan	NA	582	146	35	Yes
Attarpour [40]	2014	2011-2012	Tehran	NA	182	114	40	Yes
Amin [41]	2016	2014-2015	Ahvaz	196	NA	3	0	No

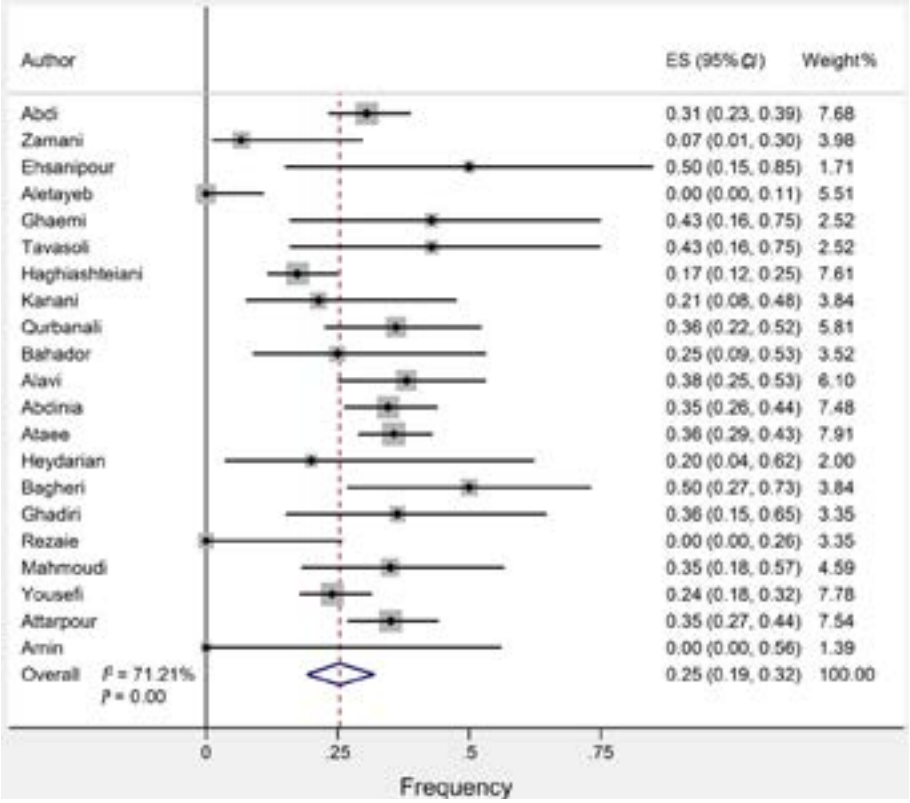

Figure 2. Forest plots of studies, investigating the frequency of *S. pneumoniae* in patients with bacterial meningitis.

3.3. Risk of bias assessment

Based on the quality assessment of the included studies, all studies were identified as having a low risk of bias (quality assessment score >7).

3.4. Frequency of S. pneumonia

The pooled frequency of *S. pneumoniae* among patients with confirmed bacterial meningitis was 25.0% (95%*CI*: 19.0-32.0; I^2=71%) (Figure 2). While it was not possible to do a formal analysis of age-stratified data due to the sample size, there did appear to be variation in the frequency of pneumococcus as a cause of bacterial meningitis by age group. Among < 1-month-old children, just 1 case of bacterial meningitis out of 46 (2.2%) was due to pneumococcus. In contrast, among those age >14 years, 68/197 (34.5%) cases were pneumococcal. Pneumococcus was of intermediate importance as a cause of bacterial meningitis in children age (1-24) months (4/38; 10.5%) and (5-14) years (3/33, 9.1%).

3.5. Frequency of other bacterial meningitis

The pooled frequency of *Haemophilus influenzae*, *Neisseria meningitidis*, *Escherichia coli*, *Klebsiella pneumoniae* and *Staphylococcus aureus* among patients with bacterial meningitis was: 17.2% (95%*CI*: 11.4-26.0), 17.1% (95%*CI*: 10.0-29.4), 9.4% (95%*CI*: 7.2-12.2), 8.0% (95%*CI*: 4.0-19.0) and 6.4% (95%*CI*: 4.2-9.8), respectively.

3.6. Patient's outcome and clinical presentation

The mortality rate among patients with bacterial meningitis was 20.4% (95%*CI*: 12.1-34.3, *n*/*N*: 66/318). The most clinical presentation of patients with bacterial meningitis was nausea (89.2%, 95%*CI*: 43.0-184.0, *n*/*N*: 224/282), lethargy (45.4%, 95%*CI*: 27.5-74.8, *n*/*N*: 51/122) and seizures (23.2%, 95%*CI*: 10.2-53.0, *n*/*N*: 74/334), respectively.

3.7. Heterogeneity and bias

As it is presented in the Galbraith plot in Figure 3, one study was seen outside the range between -2 and 2 and considered as the major source of heterogeneity. As per Begg's (P=0.1) and Egger's (P=0.7), there was no evidence of publication bias.

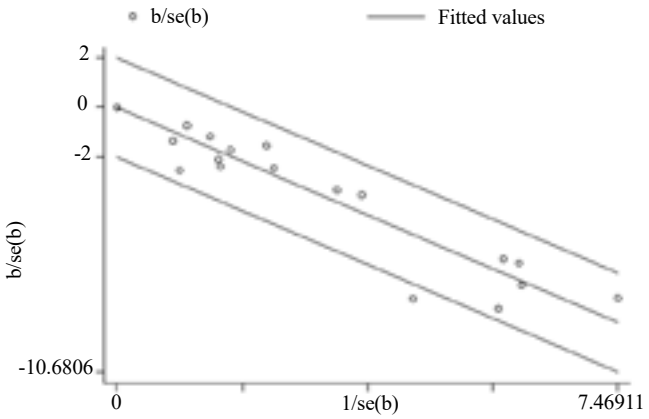

Figure 3. Galbraith plot of the frequency of *S. pneumoniae* in patients with bacterial meningitis (The study outside the range between -2 and 2 was seen as the outlier and the major source of heterogeneity).

4. Discussion

Bacterial meningitis continues to be a serious cause of death in all age groups worldwide[42,43]. In Iran, despite the improvement of infection control and therapeutic strategies, bacterial meningitis still remains a major public health problem. Based on previous studies in Iran[44,45], pneumococcus is the most common bacterium isolated from patients with meningitis. In the current systematic review and meta-analysis, we show the results of 16 years of pneumococcal meningitis surveillance in Iran. Our analyses showed that the prevalence of bacterial meningitis caused by *S. pneumoniae* was 25.0%.

Several studies have reported on the prevalence of *S. pneumoniae* around the world. For example, according to studies from Pakistan, France, Kuwait and USA, the prevalence of *S. pneumoniae* among meningitis cases was 38.5%, 29%, 40%, and 33%, respectively[46-49]. The different prevalence of *S. pneumoniae* in bacterial meningitis in Iran may be due to lack of an efficient vaccination program to control and prevent pneumococcal meningitis. Due to the epidemiology of pneumococcus, children and adults are the main target populations for pneumococcal vaccines[50].

Currently, there are two types of PCV available on the global market, synflorix (PCV10) and prevnar 13 (PCV13), which is linked to carrier proteins[51,52]. PCV10 and 13 protect against ten (1, 4, 5, 6B, 7F, 9V, 14, 18C, 19F and 23F) and thirteen (1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 23F) serotypes of pneumococcus, respectively[53-55]. The PCV serotypes are among the main and common causes of pneumococcal meningitis infection in children[51,56]. The remarkable reduction of the incidence rate of pneumococcal meningitis among children after PCV vaccination in developed countries has been demonstrated previously, which testified the effectiveness of these vaccines[37,38]. Different pneumococcal vaccines have been used in different countries, with the choice depending on which serotypes dominate in a particular location and the cost of the vaccines[57,58]. The most common serotypes isolated from pneumococcal meningitis in our country were 18, 14, 19A, 6A, 7F, 4, 3, 9V, 23F and 5[45,56,59], which are covered by the 13-valent PCV[60,61]; hence, the use of the PCV13 for general coverage of pneumococcal meningitis infections are recommended.

The frequency of antibiotic-resistant pneumococcal strains is increasing worldwide, with some variations between different countries[62,63]. Also, based on the results of previous studies, resistance to macrolides has been observed among pneumococcal strains isolated from children with pneumococcal meningitis[64]. Moreover, antibiotic-resistance is more common among vaccine serotypes[51]. Hence, the use of PCVs can be the best option for both preventions of pneumococcal meningitis and for reducing the frequency of antibiotic resistance in the short term.

Neurologic abnormalities occur with increased frequency in those who have had bacterial meningitis. Thus, the causes of the death resulted from pneumococcal meningitis may be due to the neurological complications[65]. Based on the study conducted by Kastenbauer *et al*, more than half of the patients had meningitis-associated intracranial complications (*e.g.* seizures, arterial cerebrovascular complications, brain swelling, and hydrocephalus) [66]. Furthermore, they reported that seizures, cerebrovascular complications, brain swelling, and hydrocephalus were associated with adverse outcome[66]. Østergaard *et al*, has also indicated that most of the patients with bacterial meningitis had neurological sequelae (*i.e.* neurological deficits)[65]. Likewise, in the current study, several patients developed neurological abnormalities during the clinical course of the disease (*i.e.* seizures developed in 74 of 334 episodes). Seizures as one of the most important neurological complications, the incidence (23%) of it was very similar to that of previous studies on pneumococcal meningitis[66,67].

There were some limitations to this study which should be discussed. First, as a systematic review, the existence of potential publication bias should be considered. Second, it cannot fully represent the prevalence of *S. pneumoniae* in bacterial meningitis in Iran because the extent of *S. pneumoniae* has not yet been examined in many regions of the country. Third, being a prevalence survey, this study is unable to determine risk factors for *S. pneumoniae* colonization or infection. Forth, the proportion of pneumococcus with reduced penicillin susceptibility could not be analyzed because of the limited information obtained from the studied articles.

In conclusion, the high percentage of bacterial meningitis in Iran caused by pneumococcus merits further attention from health authorities, physicians, and microbiologists. The regular surveillance of meningitis infection and the deployment of an effective vaccine may help to reduce the burden of meningitis in Iran.

Conflict of interest statement

The authors report no conflict of interest.

References

[1] Cohen R, Levy C, Bingen E, Bechet S, Derkx V, Werner A, et al. [Nasopharyngeal carriage of children 6 to 60 months during the implementation of the 13-valent pneumococcal conjugate vaccine]. *Arch Pediatr* 2012; **19**(10): 1132-1139.

[2] Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin Microbiol Rev* 2011; **24**(3): 557-591.

[3] Sharma D, Baughman W, Holst A, Thomas S, Jackson D, da Gloria Carvalho M, et al. Pneumococcal carriage and invasive disease in children before introduction of the 13-valent conjugate vaccine: comparison with the era before 7-valent conjugate vaccine. *Pediatr Infect Dis J* 2013; **32**(2): e45-53.

[4] Bijlsma MW, Brouwer MC, Kasanmoentalib ES, Kloek AT, Lucas MJ, Tanck MW, et al. Community-acquired bacterial meningitis in adults in the Netherlands, 2006–14: a prospective cohort study. *Lancet Infect Dis* 2016; **16**(3): 339-347.

[5] Stanek RJ, Mufson MA. A 20-year epidemiological study of pneumococcal meningitis. *Clin Infect Dis* 1999; **28**(6): 1265-1272.

[6] McGill F, Heyderman RS, Panagiotou S, Tunkel AR, Solomon T. Acute bacterial meningitis in adults. *Lancet* 2016; **388**(10063): 3036-3047.

[7] Ouchenir L, Renaud C, Khan S, Bitnun A, Boisvert A-A, McDonald J, et al. The Epidemiology, management, and outcomes of bacterial meningitis in infants. *Pediatrics* 2017; e20170476.

[8] Shinjoh M, Yamaguchi Y, Iwata S. Pediatric bacterial meningitis in Japan, 2013–2015–3–5 years after the wide use of *Haemophilus influenzae* type b and *Streptococcus pneumoniae* conjugated vaccines. *J Infect Chemother* 2017; **23**(7): 427-438.

[9] Stewart SS. Key points review of meningitis. *Physician Assistant Clinics* 2017; **2**(2): 177-190.

[10]Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. *Clin Microbiol Rev* 2010; **23**(3): 467-492.

[11]Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial meningitis in the United States, 1998–2007. *N Engl J Med* 2011; **364**(21): 2016-2025.

[12]Rezai MS, Ghaffari J, Mahdavi M, Bahari A, Ala S. Antibody response to 13-valent pneumococcal conjugate vaccine and 23-valent pneumococcal polysaccharide vaccine in asplenic patients with thalassemiam major: A randomized clinical trial study. *Caspian J Internal Med* 2017; **8**(1): 16-22.

[13]Kim L, McGee L, Tomczyk S, Beall B. Biological and epidemiological features of antibiotic-resistant *Streptococcus pneumoniae* in pre-and post-conjugate vaccine eras: a United States perspective. *Clin Microbiol Rev* 2016; **29**(3): 525-552.

[14]Tabatabaei SR, Rahbar M, Alam AN, Fallah F, Hashemi A, Yousefi M, et al. Detection of pbp2b gene and antimicrobial susceptibility pattern of *Streptococcus pneumoniae* isolates in Tehran hospitals, Iran. *Arch Pediatr Infect Dis* 2016; **5**(1). DOI:10.5812/pedinfect.38891.

[15]Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; **10**(5): 317-328.

[16]Demmler-Harrison DGJ, Cherry JD, Hotez PJ, Kaplan SL, Steinbach WJ. *Feigin and Cherry's textbook of pediatric infectious diseases*. In: Demmler GJ, (ed). Philadelphia, PA: Saunders; 2019.

[17]Davis S, Feikin D, Johnson HL. The effect of *Haemophilus influenzae* type B and pneumococcal conjugate vaccines on childhood meningitis mortality: a systematic review. *BMC public health* 2013; **13**(Suppl 3): S21.

[18]Tsai CJ, Griffin MR, Nuorti JP, Grijalva CG. Changing epidemiology of pneumococcal meningitis after the introduction of pneumococcal conjugate vaccine in the United States. *Clin Infect Dis* 2008; **46**(11): 1664-1672.

[19]Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLoS Med* 2009; **6**(7): e1000097.

[20]Institute JB. *Joanna Briggs Institute reviewers' manual:* 2011 edition. Adelaide, South Australia: University of Adelaide; 2011.

[21]Abdi L, Mohraz M, Hajseyed J. Acute bacterial meningitis in adults and factors influencing mortality and sequelae. *Tehran University Med J* 2006; **63**(12): 1025-1031.

[22]Zamani A Zamani F. Cerebrospinal fluid findings in neonatal bacterial meningitis. *Med J Islam Repub Iran* 2005; **19**(3): 241-245.

[23]Ehsanipour F, Khodapanahandeh F, Aslani Z. The prevalence of meningitis in children with febrile seizure hospitalized at Hazrat Rasoul Hospital (1997-2002). *Razi J Med Sci* 2005; **11**(44): 907-911.

[24]Aletayeb MH, Ahmad FS, Masood D. Eleven-year study of causes of neonatal bacterial meningitis in Ahvaz, Iran. *Pediatr Int* 2010; **52**(3): 463-466.

[25]Ghaemi E, Abdilmohammadi L, Mansourian A, Behnampour N, Tondkar R. Clinical and paraclinical findings in 100 suspicious meningitis patients. *J Gorgan Univ Med Sci* 2001; **3**(1): 17-23.

[26]Tavasoli A, Afsharkhas L, Edraki A. Frequency of meningitis in children presenting with febrile seizures at Ali-Asghar Children's Hospital. *Iran J Child Neurol* 2014; **8**(4): 51-56.

[27]Haghiashteiani M, Mohammadi-Yeganeh S, Soroush S, Sadeghifard N, Sayadi S, Dabyri H, et al. Frequency and antimicrobial susceptibility of *Haemophilus influenzae* Type b isolated from children suspected to meningitis. *Iran J Public Health* 2008; **37**(4): 52-58.

[28]Qurbanalizadegan M, Ranjbar R, Ataee R, Hajia M, Goodarzi Z, Farshad S, et al. Specific PCR assay for rapid and direct detection of *Neisseria meningitidis* in cerebrospinal fluid specimens. *Iran J Public Health* 2010; **39**(4): 45-50.

[29]Kanani S Moradi G. Epidemiological survey of acute meningitis in Kurdistan province from 1381 to the end of 1383. *Sci J Kurdistan Univ Med Sci* 2005; **10**(2):59-54.

[30]Bahador M, Amini M, Bahador M. Common cause and cerebrospinal fluid changes of acute bacterial meningitis. *Iran J Pathol* 2009; **4**(2): 75-79.

[31]Alavi S, Moshiri N, Shokri S. Evaluation of epidemiological, clinical and laboratory findings of admitted patients with meningitis in infectious diseases ward of Razi Hospital, Ahvaz. *Jundishapur Sci Med J* 2010; **9** (3): 221-231.

[32]Abdinia B, Rezaee MA, Oskouie SA. Etiology and antimicrobial resistance patterns of acute bacterial meningitis in children: a 10-year referral hospital-based study in northwest Iran. *Iran Red Crescent Med J* 2014; **16**(7): e17616. DOI:10.5812/ircmj.17616.

[33]Ataee RA, Mehrabi-Tavana A, Izadi M, Hosseini SMJ, Ataee MH. Bacterial meningitis: a new risk factor. *J Res Med Sci* 2011; **16**(2): 207.

[34]Heydarian F, Ashrafzadeh F, Rostazadeh A. Predicting factors and prevalence of meningitis in patients with first seizure and fever aged 6 to 18 months. *Neurosciences* 2014; **19**(4): 297.

[35]Bagheri-Nesami M, Babamahmoodi F, Nikkhah A. Types, risk factors, clinical symptoms and diagnostic tests of acute adult meningitis in northern iran during 2006-2012. *J Clin Diagn Res* 2015; **9**(5): IC01-IC05.

[36]GHadir K, Rezaei M, Madani A. A comparison of leukocyte adhesiveness aggregation test in blood and cerebral spinal fluid for differentiating cacterial and viral meningitis. *Clin Care J* 2015; **2**(1): 8-16.

[37]Rezaei M, Mamishi S, Mahmoudi S, Pourakbari B, Khotaei G, Daneshjou K, et al. Cerebrospinal fluid ferritin in children with viral and bacterial meningitis. *Br J Biomed Sci* 2013; **70**(3): 101-103.

[38]Mahmoudi S, Zandi H, Pourakbari B, Ashtiani MTH, Mamishi S. Acute bacterial meningitis among children admitted into an Iranian referral

children's hospital. *Jpn J Infect Dis* 2013; **66**(6): 503-506.

[39]Yousefi M Esmaeili R. Study of bacterial agents of meningitis in children and detection of their antibiotic resistance patterns in Hamadan, Western Iran. *Int J Med Invest* 2014; 3(1): 18-24.

[40]Attarpour-yazdi MM, Ghamarian A, Mousaviehzadeh M, Davoudi N. Identification of the serotypes of bacterial meningitis agents; implication for vaccine usage. *Iran J Microbiol* 2014; **6**(4): 211-218.

[41]Amin M, Ghaderpanah M, Navidifar T. Detection of *Haemophilus influenzae* type b, *Streptococcus agalactiae*, *Streptococcus pneumoniae* and *Neisseria meningitidis* in CSF specimens of children suspicious of meningitis in Ahvaz, Iran. *Kaohsiung J Med Sci* 2016; **32**(10): 501-506.

[42]Park BS, Kim SE, Park SH, Kim J, Shin KJ, Ha SY, et al. Procalcitonin as a potential predicting factor for prognosis in bacterial meningitis. *J Clin Neurosci* 2017; **36**: 129-133.

[43]Houri H, Pormohammad A, Riahi SM, Nasiri MJ, Fallah F, Dabiri H, et al. Acute bacterial meningitis in Iran: Systematic review and meta-analysis. *PloS One* 2017; **12**(2): e0169617.

[44]Mehrabi Tavana A Ataee RA. Invasive Pneumococcal disease (IPD) serotype frequency in Iranian patients. *Iran Red Crescent Med J* 2013; **15** (8): 740-742.

[45]Attarpour-yazdi MM, Ghamarian A, Mousaviehzadeh M, Davoudi N. Identification of the serotypes of bacterial meningitis agents; implication for vaccine usage. *Iran J Microbiol* 2014; **6**(4): 211-218.

[46]Zaidi AK, Khan H, Lasi R, Mahesar W, Group SM. Surveillance of pneumococcal meningitis among children in Sindh, southern Pakistan. *Clin Infect Dis* 2009; **48**(Suppl 2): S129-S135.

[47]Levy C, Varon E, Picard C, Béchet S, Martinot A, Bonacorsi S, et al. Trends of pneumococcal meningitis in children after introduction of the 13-valent pneumococcal conjugate vaccine in France. *Pediatr Infect Dis J* 2014; **33**(12): 1216-1221.

[48]Sadeq H, Husain EH, Alkoot A, Atyani S, Al-fraij A, Al-Daithan A, et al. Childhood meningitis in Kuwait in the era of post pneumococcal conjugate vaccination: A multicenter study. *J Infect Public Health* 2017; **10**(6): 766-769.

[49]Nigrovic LE, Kuppermann N, Malley R. Children with bacterial meningitis presenting to the emergency department during the pneumococcal conjugate vaccine era. *Academic Emergency Med* 2008; **15** (6): 522-528.

[50]Berical AC, Harris D, Dela Cruz CS, Possick JD. Pneumococcal vaccination strategies. An update and perspective. *Ann Am Thorac Soc* 2016; **13**(6): 933-944.

[51]Hsu HE, Shutt KA, Moore MR, Beall BW, Bennett NM, Craig AS, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *N Engl J Med* 2009; **360**(3): 244-256.

[52]Miller E, Andrews NJ, Waight PA, Slack MP, George RC. Effectiveness of the new serotypes in the 13-valent pneumococcal conjugate vaccine. *Vaccine* 2011; **29**(49): 9127-9131.

[53]Simonsen L, Taylor RJ, Young-Xu Y, Haber M, May L, Klugman KP. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalization and mortality in all age groups in the United States. *MBio* 2011; **2**(1): e00309-00310.

[54]Pilishvili T, Lexau C, Farley MM, Hadler J, Harrison LH, Bennett NM, et al. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. *J Infect Dis* 2010; **201**(1): 32-41.

[55]Nhantumbo AA, Weldegebriel G, Katsande R, de Gouveia L, Comé CE, Cuco AZ, et al. Surveillance of impact of PCV-10 vaccine on pneumococcal meningitis in Mozambique, 2013–2015. *PLoS One* 2017; **12**(6): e0177746.

[56]Houri H, Karimi A, Saee Y, Fallah F, Rahbar M, Tabatabaei SR. Distribution of capsular types and drug resistance patterns of invasive pediatric *Streptococcus pneumoniae* isolates in Teheran, Iran. *Int J Infect Dis* 2017; **57**: 21-26.

[57]Sleeman KL, Griffiths D, Shackley F, Diggle L, Gupta S, Maiden MC, et al. Capsular serotype-specific attack rates and duration of carriage of *Streptococcus pneumoniae* in a population of children. *J Infect Dis* 2006; **194**(5): 682-688.

[58]Gessner BD, Mueller JE, Yaro S. African meningitis belt pneumococcal disease epidemiology indicates a need for an effective serotype 1 containing vaccine, including for older children and adults. *BMC Infect Dis* 2010; **10**: 22.

[59]Tabatabaei SR, Fallah F, Shiva F, Shamshiri A, Hajia M, Navidinia M, et al. Multiplex PCR assay for detection of pneumococcal serotypes in nasopharyngeal samples of healthy children; Tehran, 2009-2010. *Annu Res Rev* Biol 2014; **4**(24): 3780-3790.

[60]Zaidi AK, Khan H, Lasi R, Mahesar W. Surveillance of pneumococcal meningitis among children in Sindh, southern Pakistan. *Clin Infect Dis* 2009; **48**(Suppl 2): S129-S135.

[61]Falade AG, Lagunju IA, Bakare RA, Odekanmi AA, Adegbola RA. Invasive pneumococcal disease in children aged <5 years admitted to 3 urban hospitals in Ibadan, Nigeria. *Clin Infect Dis* 2009; **48**(Suppl 2): S190-S196.

[62]Livermore DM. Bacterial resistance: origins, epidemiology, and impact. *Clin Infect Dis* 2003; **36**(Suppl 1): S11-S23.

[63]Jacobs MR, Good CE, Beall B, Bajaksouzian S, Windau AR, Whitney CG. Changes in serotypes and antimicrobial susceptibility of invasive *Streptococcus pneumoniae* strains in Cleveland: a quarter century of experience. *J Clin Microbiol* 2008; **46**(3): 982-990.

[64]Imöhl M, Reinert RR, Mutscher C, van der Linden M. Macrolide susceptibility and serotype specific macrolide resistance of invasive isolates of *Streptococcus pneumoniae* in Germany from 1992 to 2008. *BMC Microbiol* 2010; **10**(1): 299.

[65]Østergaard C, Konradsen HB, Samuelsson S. Clinical presentation and prognostic factors of *Streptococcus pneumoniae* meningitis according to the focus of infection. *BMC Infect Dis* 2005; **5**(1): 93.

[66]Kastenbauer S, Pfister HW. Pneumococcal meningitis in adults: spectrum of complications and prognostic factors in a series of 87 cases. *Brain* 2003; **126**(5): 1015-1025.

[67]Sigurdardottir B, Björnsson ÓM, Jonsdottir KE, Erlendsdottir H, Gudmundsson S. Acute bacterial meningitis in adults: a 20-year overview. *Arch Intern Med* 1997; **157**(4): 425-430.